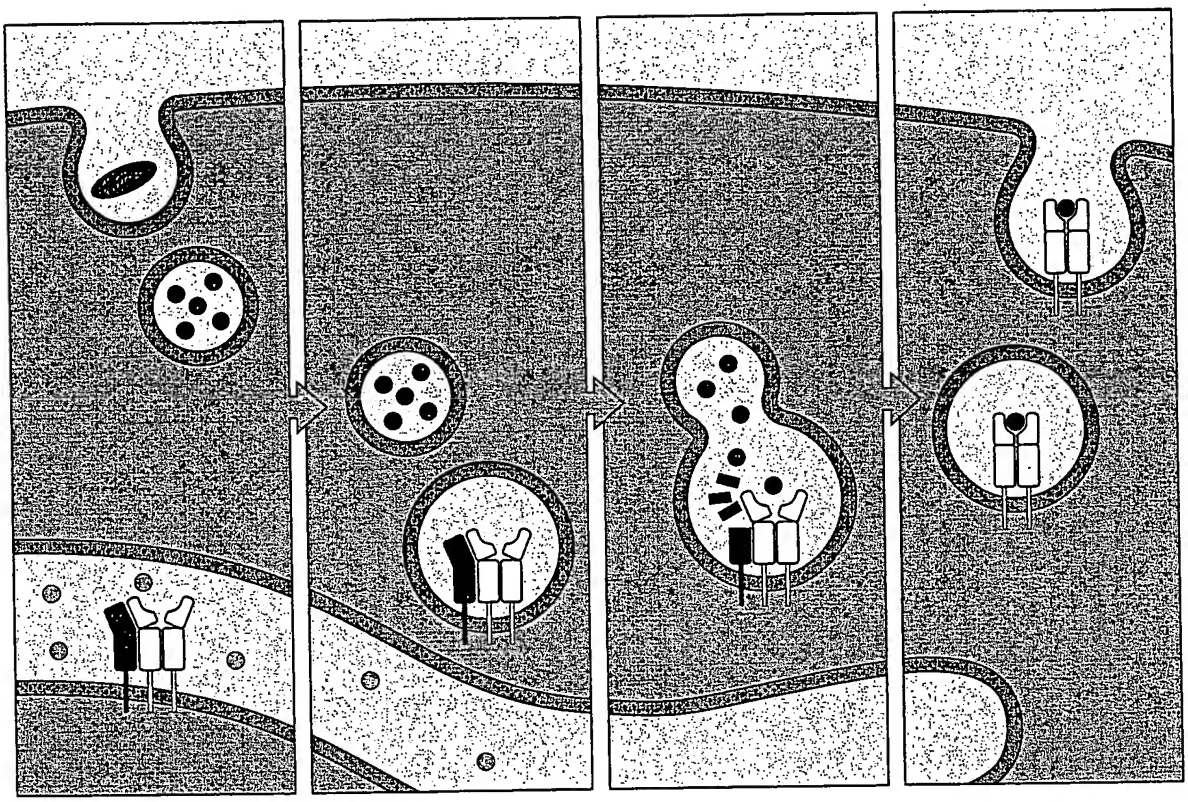
IMMUNOBIOLOGY

THE IMMUNE SYSTEM IN HEALTH AND DISEASE



JANEWAY - TRAVERS

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THE IMMUNE SYSTEM IN HEALTH AND DISEASE

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Proteolytic enzymes (proteases) that cleave polypeptide sequences at particular amino acids have been used to probe the structure of antibody molecules. Limited digestion with the protease papain cleaves antibody molecules into three fragments (Fig. 3.4). Two fragments are identical and contain the antigen-binding activity, and these are termed the **Fab fragments**, for **F**ragment **a**ntigen **b**inding. The other fragment contains no antigen-binding activity but crystallizes readily, and for this reason it is named the **Fc fragment**, for **F**ragment **c**rystallizable. The Fab fragments correspond to the arms of the antibody molecule that contain the complete light chains paired with the V_H and C_H1 domains of the heavy chains, whereas the Fc fragment corresponds to the paired C_H2 and C_H3 domains. The disulfide bridges between the heavy chains lie in the short hinge region between the C_H1 and C_H2 domains. As illustrated in Fig. 3.4, papain cleaves the antibody molecule on the amino-terminal side of the disulfide bridges, releasing the two arms of the antibody as separate Fab fragments, while the carboxy-terminal halves of the heavy chains remain linked, forming the Fc fragment. Another protease, pepsin, cleaves in the same region of the antibody molecule but on the carboxy-terminal side of the disulfide bridges (see Fig. 3.4), producing a fragment, the $F(ab')_2$ fragment, in which the two arms of the antibody molecule remain linked.

Electron microscopy of antibody complexes with a bivalent hapten capable of crosslinking two antigen-binding sites demonstrates that the hinge region is flexible and that the angle between the two Fab arms can vary (Fig. 3.5). Such flexibility is required to allow the binding of both arms of the antibody molecule to sites that are different distances apart, as occurs with sites on bacterial cell wall polysaccharides. It is thought that flexibility

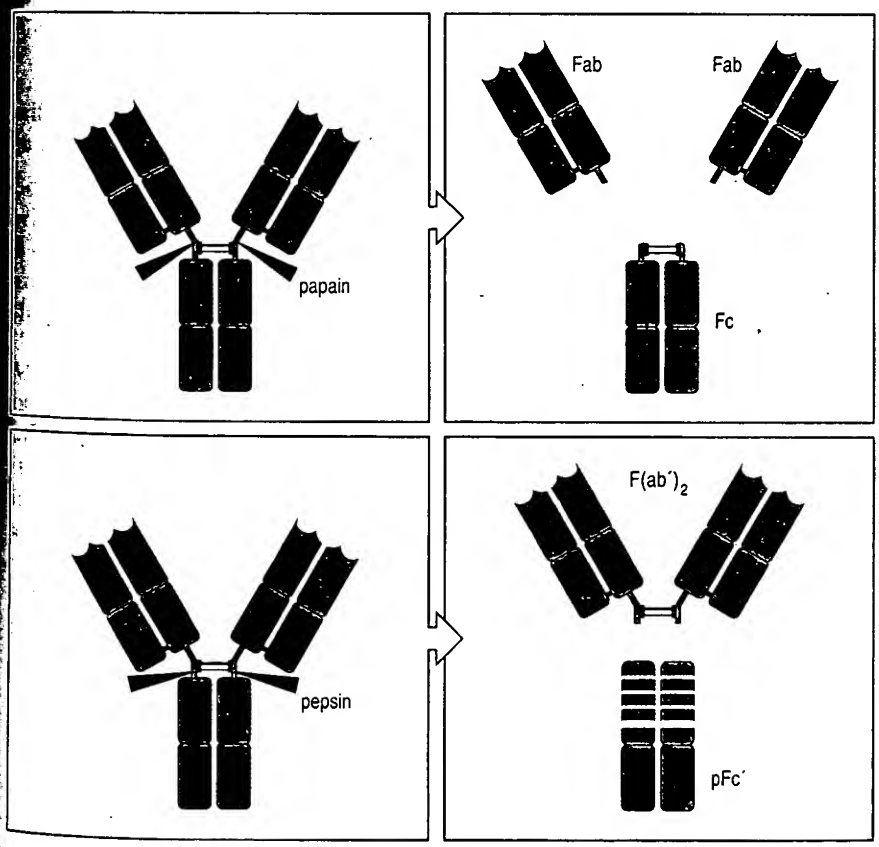

Fig. 3.4 The Y-shaped immunoglobulin molecule can be dissected by partial digestion with proteases. Papain cleaves the immunoglobulin molecule into three pieces, two Fab fragments and one Fc fragment (upper panels). Pepsin cleaves an immunoglobulin to yield one $F(ab')_2$ fragment and many small pieces of the Fc fragment, the largest of which is called the pFc′ fragment (lower panels).